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SHORT COMMUNICATIONS

# Synthesis of New 2*H*-Benzimidazole 1,3-Dioxide Derivatives Analogous to Separase Inhibitor (Sepin-1)

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**Abstract**—New biologically active 2*H*-benzimidazole 1,3-dioxide derivatives, analogs of Sepin-1, have been synthesized starting from benzofuroxan. Electrophilic substitution of hydrogen in the 2*H*-benzimidazole ring occurs at different positions, depending on the electrophile nature.

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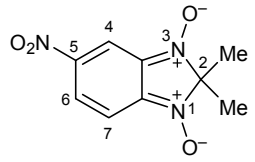
2*H*-Benzimidazole 1,3-dioxides exhibit high biological activity. They can be used as antiparasitic agents against *Tripanosoma cruzi* and *Leishmania spp.* which, according to the WHO data, have infected about 30 million people; more than 400 million people are constantly under threat of infection [1].

Do et al. [2] recently reported that 2*H*-benzimidazole 1,3-dioxide derivatives inhibit separase, a cysteine protease important in the cell division process [2]. The most active separase inhibitor was 2,2-dimethyl-5-nitro-2*H*-benzimidazole 1,3-dioxide patented as Sepin-1 [3, 4].




Sepin-1

Introduction of substituents other than methyl groups into the 2-position should enhance the inhibitory activity of 2*H*-benzimidazole 1,3-dioxides. Herein we describe the synthesis of new 2*H*-benzimidazole 1,3-dioxide derivatives that are analogs of Sepin-1.

Compound **2** was synthesized by reaction of benzofuroxane **1** with isobutyl alcohol in the presence of sulfuric acid. Presumably, the reaction involves rearrangement of primary carbocation generated from isobutyl alcohol into isomeric more stable secondary carbocation [5].

Taking into account that the inhibitory activity of compounds of this series is related to the presence of a nitro group in the 5-position of 2*H*-benzimidazole [2], 2*H*-benzimidazole 1,3-dioxide **2** was subjected to nitration with nitric acid in acetic acid. We thus obtained Sepin-1 analog **3**. Unlike the nitration, the bromination of **2** with molecular bromine in acetic acid gave 4-bromo derivative **4**. Thus, the direction of electrophilic substitution in 2*H*-benzimidazole 1,3-dioxide depends on the electrophile nature.

The structure of **4** was determined by X-ray analysis (see figure). The bond lengths in molecule **4** conform to the corresponding standard values. The heterocycle is planar, and the methyl and ethyl substituents are oriented in opposite directions with respect to the heterocycle.

**2-Ethyl-2-methyl-2*H*-benzimidazole 1,3-dioxide (2).** Isobutyl alcohol, 1 mL (0.01 mol), was added